Oesophageal Cancer in Wales

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Millar (1961), in his study of gastro-intestinal cancer in Montgomeryshire, noted an increased frequency of oesophageal and gastric cancer but not of colonic and rectal cancer in North Wales. The present study is an extension of one previously reported which connected the high frequency of gastric cancer in Wales (Ashley and Davies, 1966a) with the genetic constitution of the Welsh people. It deals with the frequency and distribution of oesophageal cancer in the Principality of Wales; oesophageal cancer, like gastric cancer, has a very high mortality, and it is therefore reasonable to regard the mortality rates for this condition as representative of the incidence rates.

Material and Methods

In the six-year period 1958 to 1963 the total number of deaths ascribed to oesophageal cancer in Wales was 1107; 563 in males and 544 in females. The number of deaths expected on the basis of the age and sex specific death rates at five-year intervals using the age distribution of the people of Wales at the 1961 census was 812.5; 481.6 in males and 330.9 in females (calculated from the data of the Registrar General, 1960, 1961, 1962a, 1963, 1964a,b, 1965). The Standardized Mortality Ratios (SMR) for the whole of the Principality were 117 for males, 164 for females, and 136 for both sexes combined. All three of these values are highly significantly greater than 100, and are indeed greater than the corresponding ratios for gastric cancer which has long been known to be more frequent in Wales than in England.

It has been pointed out (Ashley and Davies, 1966a) that Wales is an inhomogeneous country, and that there

are two moieties of the population, the Welsh and the non-Welsh, most of whom are immigrants from neighbouring England. These two groups can be separated on the basis of their ability to speak the Welsh language and also on the basis of their Welsh or non-Welsh surname (Ashley and Davies, 1966a,b; Registrar General, 1962b). The first parameter readily leads to a tripartite division of Wales into three zones. In the first, the northern and western counties, more than 70% of the population are Welsh speaking; in the third, the extreme South East, less than 10% are Welsh speaking; and in the remaining part of the country between 15 and 45% of the population speak Welsh.

Results

The three zones—high, intermediate, and low 'Welsh'—may readily be separated on the basis of the major local authority subdivisions and separate SMRs can be calculated for each (Table I). The SMRs for the high and intermediate Welsh zones for males and for females are significantly greater than 100, and in each sex there is a gradient, the highest SMR in the high Welsh zone and the lowest in the low Welsh zone.

The distribution within Wales was studied in more detail by an analysis of the data for the 13 counties and 4 county boroughs separately (Table II). All but two of the SMRs for males were greater than 100 and all of those for females were 100 or more. The highest SMRs in men were in the counties of Carmarthen, Brecon, and Merioneth, and for women in the counties of Anglesey, Caernarvon, Carmarthen, and Merioneth. The first two columns in Table II give an estimate of the degree of 'Welshness' of the area concerned. Another,

TABLE I
DEATHS FROM OESOPHAGEAL CANCER IN WALES: 1958-63

Zone	Males			Females		
	Observed	Expected	SMR	Observed	Expected	SMR
High Welsh	119	88.6	134	133	58.8	226
Intermediate Welsh	318	268.5	119	307	188.3	163
Low Welsh	126	124.5	101	104	83.8	124

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TABLE II
STANDARDIZED MORTALITY RATIOS FOR OESOPHAGEAL
CANCER: WALES 1958-63

	o/ o	o/ o	Males			Females		
			SMR Obs.	Exp.	O/E	SMR Obs.	Exp.	O/E
Anglesey	84	16	105	134	78	210	215	98
Brecon	54	46	152	120	126	180	173	104
Caernarvon	76	24	119	130	92	281	204	143
Cardigan	83	17	132	134	99	182	213	86
Carmarthen	83	17	156	134	116	220	213	103
Denbigh	70	30	128	128	100	171	195	88
Flint	38	62	123	112	110	174	151	115
Glamorgan	35	65	122	111	110	143	147	97
Merioneth	85	15	148	135	110	210	216	97
Monmouth	17	83	92	102	90	118	122	97
Montgomery	64	36	125	125	100	161	187	86
Pembroke	45	55	103	116	89	112	160	70
Radnor	20	80	70	104	67	100	126	79
Cardiff	24	76	105	105	100	139	131	106
Swansea	35	65	86	111	77	188	147	128
Newport	10	90	136	99	137	108	112	96
Merthyr Tydfil	40	60	108	113	96	169	154	110

unpublished, investigation has shown that the small local authority areas, rural and urban districts, and towns of Wales can be divided into three groups on the basis of the relation between the proportion of the people who speak Welsh and the proportion who have names included in the list of Welsh names used in this work and given in the previous papers (Ashley and Davies 1966a,b). In one group the proportion with Welsh names equals the proportion who can speak Welsh; in the second group the proportion with Welsh names is 3 times the proportion of Welsh speakers; and in the third group the proportion with Welsh names is 10 times the proportion of Welsh speakers. These three groups of areas correspond very well to the division of Wales into three zones on the basis of the frequency of Welsh speaking which has been used above. In the second and third groups of areas it is likely that many people are of Welsh ancestry but have not learned to speak and to use the Welsh language, so an estimated value for the 'Welshness' of each county and county borough has been calculated. In the low 'Welsh' zone the proportion of Welshness was assessed as 5 times the proportion of Welsh speakers, in the intermediate zone the proportion of Welshness was assessed as twice the proportion of Welsh speakers, and in the high 'Welsh' zone it was assumed that the Welsh speakers represented 9 out of 10 of the 'Welsh' in the area. The assessed values for 'Welshness' are included in Table II rounded off to the nearest whole number.

Computations. The SMRs for the Welsh and non-Welsh components of the population of Wales have been calculated from the data in Table II for each sex separately by the method of least squares.

For males the SMR for the Welsh is 142 and for the non-Welsh 94. For females the corresponding values are 237 and 98. In either sex the SMR for the 'Non-Welsh' people of Wales corresponds closely to that for England and Wales as a whole, while in each sex the SMR for the 'Welsh' of Wales is significantly higher than that for the 'Non-Welsh'. Columns 4 and 7 of Table II show the expected SMR for males and females after the calculated SMRs for the Welsh and non-Welsh have been multiplied by the factors in columns 1 and 2, and columns 5 and 8 show the ratio between the observed and the expected SMR for each county or county borough. The range of SMRs has reduced, and none of the values in columns 5 and 8 is significantly different from 100. None of the areas shows a value greater than 110 for both males and females, and the apparent excess of cases in males in Brecon and Newport and in females in Caernarvon and Swansea may be due to random variations. The counties of Pembroke and Radnor show values of the SMR which are lower than expected in both males and females. These are not contiguous counties. Radnor is a farming county which abuts on the English county of Shropshire, and my assessment that the population is 20% 'Welsh' may be too high. Pembroke, the most westerly county of South Wales is itself divided into North and South, with a marked difference in the frequency of Welsh speaking, and it may also be that the estimate of the degree of 'Welshness' for this county is erroneous.

It is possible to calculate from the data of Table II the expected numbers of deaths from oesophageal cancer in the three zones of Wales, taking into account the proportion of individuals regarded as

TABLE III
ADJUSTED STANDARDIZED MORTALITY RATIOS FOR
OESOPHAGEAL CANCER

Zone	Male			Female		
	Cases		SMR	Cases		SMR
	Observed	Expected		Observed	Expected	
High	119	117.7	101	133	125	106
Intermediate	318	307	104	307	297	103
Low	126	122	103	104	104	100

Welsh in each zone (Table III). In each zone the difference from 100 has been reduced to a very small value. The calculations for Table II do not take into account the relative sizes of the local authority areas whereas those in Table III do so.

The second method of analysis is based on the frequency with which patients suffering from the disease were found to have Welsh surnames (Ashley and Davies, 1966a). This method is generally applicable only to males because married women assume their husband's surname. Data were available from 129 patients with oesophageal cancer seen at this hospital during the past 10 years. The number with Welsh surnames, 78, was greater than that expected from a study of the electoral registers of the area, 74, but the difference was not statistically significant. It is possible to calculate the proportion of men with Welsh surnames to be expected in a population with a disease such as this. Let w equal the proportion in the general population with Welsh names, then $(1-w)$ is the proportion with non-Welsh surnames. If k is the chance that a man with a non-Welsh name will develop oesophageal cancer and ak is the chance that a man with a Welsh name will develop the disease the total number of cases will be:

$$akw + k(1-w)$$

and the proportion with Welsh names in the sample of individuals with oesophageal cancer will be:

$$\frac{akw}{akw + k(1-w)}$$

The factor k cancels out of this equation. The relative risk of the Welsh compared to the non-Welsh is $142/94$, $a=1.51$, and the proportion w in the population with Welsh names is $74/129=0.57$, $(1-w)=0.43$. The expected proportion with Welsh names can then be calculated as 0.67 and the expected number from a population of 129 cases is 86. The observed number of 78 cases with Welsh names falls between the two expected values and is not significantly different from either. If the town

of Swansea is taken alone the total observed number of cases was 46 of whom 24 had Welsh names. The proportion of the population in Swansea with Welsh names is 0.44. Repeating the calculation above using $w=0.44$, $a=1.51$, the number expected with Welsh names is 25, only one more than the observed number. The numbers of cases are small for this type of analysis and the most that can be said is that the data from the surnames are consistent with those from the geographical distribution.

Sex differences. A striking and unexpected feature of the findings in this investigation has been the disparity between males and females. A similar investigation of gastric cancer (Ashley and Davies, 1966a; Ashley, 1969) has shown that the relative risk of developing this tumour in men is 1.67 for the Welsh against the non-Welsh of Wales and 1.43 in women. For oesophageal cancer the relative risks are 1.51 for men and 2.42 for women. The ratio of the SMRs is 0.59 in the high 'Welsh' zone, 0.73 in the intermediate zone, and 0.81 in the low 'Welsh' zone.

Most of the deaths from oesophageal cancer, 63% in males and 69% in females, occur after the age of 65 years, and an approximation to the ratio between the rates in males and females can be made if the formula:

$$\frac{\text{Cases in Males} \times (\text{Female pop}^n > 65)}{\text{Cases in Females} \times (\text{Male pop}^n > 65)}$$

is used. This formula gives a closer approximation to the relative frequency in the two sexes in the various parts of the country than does a simple ratio between the gross death rates. The data for the standard regions for the years 1961-3 are set out in Table IV and show quite clearly that this is a difference in mortality experience which is specific to Wales. I have carried out similar calculations for the counties and county boroughs of England and Wales using the data published by the Registrar General (1963, 1964a,b, 1965, 1966). With the small numbers of cases in many of the towns and

TABLE IV
DEATHS FROM CARCINOMA OF OESOPHAGUS IN THE STANDARD
REGIONS OF ENGLAND AND WALES 1961-4

	Population > 65 × 10 ³		Deaths Cancer of Oesophagus		Ratio of Gross Death rates
	Male	Female	Male	Female	
England and Wales	2146	3513	5471	4360	2.05
<i>Region</i>					
Northern	146	218	372	304	1.28
East and West Riding	188	306	418	283	2.43
North West	291	501	857	704	2.10
North Midlands	168	253	376	286	1.99
Midlands	190	302	544	370	2.37
Eastern	178	275	396	322	1.98
London and South Eastern	526	929	1363	1019	2.35
Southern	139	224	339	285	1.92
South West	188	300	466	398	1.86
Wales	131	205	350	389	1.34
Wales I	89	129	239	240	1.45
Wales II	42	66	111	149	1.15

smaller counties, there is naturally a wide range in the calculated ratio between the rates. The standard error of each ratio was estimated by dividing it by the square root of the smaller number of deaths, male or female. The ratio was considered significantly different from that for the whole country if it differed by more than two standard errors. Significantly high values were found only in the county of Kent and in the West Riding of Yorkshire. Significantly low values were found for the counties of Buckingham, Cornwall, Hereford, the Holland division of Lincolnshire, Oxfordshire, and Westmoreland, and the county boroughs of Barrow, Bath, Birmingham, Canterbury, Croydon, Dewsbury, Plymouth, St. Helens, and Southport in England, and the counties of Caernarvon, Cardigan, Carmarthen, Denbigh, Flint, Merioneth, Monmouth, Pembroke, and Radnor, and the town of Swansea in Wales. If, because of the imprecision of the estimate, the standard for recognition of significance is raised to a difference of 3 standard errors, the counties of Cornwall and Hereford and the towns of Barrow, Bath, Birmingham, Canterbury, and Plymouth in England, and the counties of Carmarthen, Denbigh, Flint, Pembroke and Radnor in Wales remain as showing a significantly low ratio between the rates for males and females.

In the standard regions, the ratio between the rates is significantly high in the regions East and West Riding, Midlands, and London and South Eastern, and is significantly low only in Wales.

One of the counties with a low ratio, Hereford, is contiguous with the Welsh counties of Brecon and Radnor, and another, Cornwall, is also part of the Celtic fringe of the United Kingdom. No pattern is apparent in the distribution of the remaining areas of low male to female ratio.

Discussion

There is a greater death rate from oesophageal cancer in Wales than in England. This difference is more marked in females than in males. Detailed examination of the distribution of deaths from this cause within the Principality supports the thesis that the difference is due to factors inherent in 'Welshness', i.e. that the Welsh have a greater susceptibility to this disease than do their English cousins because of differences in the gene pools of the two groups of individuals.

The much greater mortality in the women of Wales is an interesting and unusual feature. In the previous investigation of gastric cancer (Ashley and Davies, 1966a; Ashley, 1969), the increased susceptibility to the disease in the Welsh was shared by the two sexes almost equally and within the United Kingdom is peculiar to the Principality of Wales. The three regions, the East and West Riding of Yorkshire, the Midlands, and London and South Eastern in which there is a deficiency of cases of oesophageal cancer in women relative to men show specifically a low death rate in women, the rate in men being slightly below or equal to that in the country as a whole.

The recent U.I.C.C. publication, Cancer Incidence in Five Continents (Doll, Payne, and Waterhouse, 1966), gives age-adjusted mortality rates, based on the age distribution in the world population and that in the European population. The values of these age-adjusted rates and the ratios between them are given for the 10 countries in which the numbers of cases is greatest. In most instances the ratio between the age-adjusted rates is greater than that for England and Wales, the single exception being Finland which, like Wales, shows a high

TABLE V
AGE-ADJUSTED DEATH RATES FOR OESOPHAGEAL CANCER
FROM CANCER INCIDENCE IN FIVE CONTINENTS

Country	Age-adjusted Death Rate per 100,000					
	World Population			European Population		
	Male	Female	M/F	Male	Female	M/F
Chile	10.7	5.0	2.14	15.5	7.0	2.22
Puerto Rico	18.0	7.7	2.34	26.1	11.2	2.33
Connecticut	6.0	1.0	6.0	8.7	1.5	5.8
New York State	4.2	1.0	4.2	6.3	1.6	3.94
Singapore (Chinese)	11.9	2.0	5.95	16.2	2.7	6.0
Denmark	3.6	1.6	2.25	5.6	2.7	2.08
England and Wales	4.5	2.4	1.87	6.9	3.6	1.92
Finland	7.1	5.8	1.22	10.7	9.1	1.17
Norway	3.3	0.8	4.12	5.1	1.2	4.25
Sweden	2.5	1.2	2.08	3.8	1.9	2.00

rate in men and a much higher one in women. Finland contrasts with the adjacent Scandinavian countries of Norway and Sweden in much the same way as Wales contrasts with England. On the other hand the Chinese of Singapore show a very high rate in males and a much lower rate in females (Table V).

The high rates for males in Chile, Puerto Rico, Singapore, and Finland, and for females in Chile, Puerto Rico, and Finland may be related to different dietary and culinary habits in these parts of the world, though it would be necessary to suggest a great difference in the eating habits of the men and women of the Chinese community of Singapore.

Within the United Kingdom and particularly within Wales dietary differences are not profound and there is little difference between the diets of males and females. A possible explanation lies in the association with iron-deficiency anaemia (Oetlté, 1967). This in turn is commoner in women than men and may be associated with achlorhydria which in turn may be due to genetic causes. Kilpatrick (1961), however, showed that there was no significant difference between the mean values for haemoglobin, packed cell volume, and serum iron between men from Wensleydale in the North Riding of Yorkshire, and men, both miners and non-miners, from the Rhondda in South Wales, and also that there was no difference in these indexes between women from Wensleydale and women from the Rhondda. A more recent survey (Campbell *et al.*, 1968) showed no differences in haemoglobin levels in the six Welsh areas, Newport, Abertillery, Aberdare, East Flint, Monmouth, and Brecon.

If the difference is genetic in origin, the wide disparity between the experiences of Welsh men and Welsh women suggests that it may be related to genes on the X chromosome which are dominant in character. A woman, having two X chromosomes, would have a much higher chance of having such genes than a man, and the frequency of cancer of this

site might therefore be expected to vary more in women than in men. This is indeed the case. The SMR for oesophageal cancer in the major local authority areas of Wales ranges from 70 to 156, while that for women ranges from 100 to 281 (Table II), and in the Standard regions of England the range is from 86 to 114 in men and from 80 to 118 in women. It is tempting to speculate that this may be related to a difference in immunological capacity, as it is suggested that genes on the X chromosomes are involved in the abnormal mechanisms leading to the development of auto-immune diseases such as Hashimoto's disease and disseminated lupus erythematosus, which are commoner in women than in men (Burch, 1966).

Summary

Data are presented on the death rates from oesophageal carcinoma in Wales. There is a higher mortality from this cause in Wales than in England, and the difference can be related to 'Welshness' estimated from the parameters Welsh speaking and Welsh names. The excess mortality is much greater in women than in men.

It is suggested that the higher mortality from this condition is related to genetic factors, i.e. that because of differences in the gene pool the Welsh are more liable to develop this neoplasm than the non-Welsh.

It is considered unlikely that the excess mortality in women is related to iron-deficiency anaemia or to achlorhydria which are not more prevalent in the more 'Welsh' parts of Wales. It is tentatively suggested that a possible explanation may be that factors associated with genes carried on the X chromosome are concerned in carcinogenesis.

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